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Review

Transplantation of Umbilical Cord Blood–Derived Cells for Novel Indications in Regenerative Therapy or Immune Modulation: A Scoping Review of Clinical Studies

Marco A.J. Iafolla [1], Jason Tay [2,3], David S. Allan [1,3,*]

[1] *Regenerative Medicine Program*
[2] *Clinical Epidemiology Program, Ottawa Hospital Research Institute*
[3] *Blood & Marrow Transplantation Program, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada*

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A B S T R A C T

Although used mainly for transplantation of hematopoietic stem cells in the treatment of blood disorders, umbilical cord blood (UCB)-based therapies are now being used increasingly for novel applications in non-hematopoietic diseases and as a form of cellular regenerative therapy or immune modulation. We performed a systematic scoping review by searching Medline, EMBASE, and the Cochrane Library for published articles, and we searched www.clinicaltrials.com and the World Health Organization International Clinical Trials Registry Platform to describe the breadth of published studies and ongoing clinical activity in umbilical cord-based cellular therapy for regenerative therapy and immune modulation. The most commonly published area of expertise in the use of UCB-derived cellular transplantation for novel indications is for neurological disorders and this remains the most active area of study in ongoing registered trials. An increasingly broad range of disorders, however, are reflected in ongoing registered trials, which suggests greater activity, interest, and investment in UCB-derived cellular therapy. Interestingly, adult patients compose the majority of patients reported in published reports and registered ongoing clinical studies continue to enroll predominantly adult subjects. Geographically, Asian countries appear most active in UCB-derived cellular therapy and our analysis of ongoing studies suggests this trend will likely continue. Regular assessment of published and ongoing activity in UCB transplantation for emerging novel indications will be critical for informing UCB banking establishments and funding agencies to guide changes in banking practices related to emerging trends in cell therapy.

INTRODUCTION

Transplantation of cells derived from human umbilical cord blood (UCB) has demonstrated increasing promise in the treatment of both malignant and nonmalignant diseases [1-3]. Following the first successful transplantation of UCB in 1988 for the treatment of Fanconi's anemia [4], the past decades have led to increased use of cord blood as a source of cells for hematopoietic stem cell transplantation to treat a range of hematological and nonhematolgioical diseases [5]. UCB also contains nonhematopoietic stem and progenitor cells capable of differentiating into epithelial [6] or endothelial cell progenitors [7,8], mesenchymal stromal cells (MSCs), unrestricted somatic stem cells [9], and neural progenitor cells [10]. The therapeutic potential of stem and progenitor cells in UCB to treat a broad range of disorders has led to increasing use of UCB transplantation to treat patients with nonhematopoietic diseases, including applications in regenerative therapy and modulation of refractory autoimmune diseases.

UCB cells can be cryopreserved and stored for years without significant loss of viability, making them readily available for immediate transplantation in most instances [11,12]. Public banking of UCB has become more widespread in many parts of the world [13], providing easy access to UCB units from worldwide registries [12]. Private banking of cord blood is also available in many jurisdictions. The increased demand for UCB banking has led to the development of regulatory bodies for quality control, including the American Association of Blood Banks and the Foundation for Accreditation of Cellular Therapy [14,15].

Although used mainly for transplantation of hematopoietic stem cells in the treatment of blood disorders, UCB-based therapies are now being used increasingly for novel applications in nonhematopoietic diseases and as a form of cellular regenerative therapy or immune modulation. In this systematic scoping review, we describe the breadth of published studies and ongoing clinical activity in umbilical cord-based cellular therapy for regenerative therapy and immune modulation. Our primary goal was to identify current trends in cell-based therapy using UCB that would inform cord blood banking establishments and transplantation centers regarding current and emerging trends related to methods of cell manipulation and indications for using cord blood in regenerative medicine and immune modulation.

MATERIALS AND METHODS

Searching for Relevant Published Trials

We sought to identify studies that described the use of human UCB to treat patients for nonconventional indications that addressed regenerative therapy or modulation of immune disorders. A systematic scoping review of all published trials was performed in accordance with guidelines suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [16]. We performed a search on the following databases using the OVID interface: (1) MEDLINE (1950 to week 26 of 2012), (2) EMBASE (1980 to

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* Correspondence and reprint requests: David S. Allan, MD, FRCP(C), Ottawa Hospital Research Institute, Box 704, 501 Smyth Rd., Ottawa, ON, Canada K1H 8L6.

E-mail address: daallan@ohri.ca (D.S. Allan).

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Search Strategy:

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1 Fetal Blood/cy, tr (5693)
2 fetal blood/ and Hematopoietic Stem Cell Transplantation/ (1115)
3 Cord Blood Stem Cell Transplantation/ (1875)
4 uc blood.tw. (50)
5 (umbilical adj2 blood).tw. (8402)
6 (cord adj2 blood).tw. (19258)
7 (placenta$ blood adj2 transplant$).tw. (17)
8 or/1-7 (22852)
9 Regenerative Medicine/ (2141)
10 exp Regeneration/ (157579)
11 regener$.tw. (104758)
12 Basilar Artery/su or (basilar adj2 arter$ dissection$).tw. (505)
13 Ischemia/ or (Limb$ adj2 ischemia$).tw. (44373)
14 Cardiomyopathy, Dilated/ or (congestive adj2 cardiomyopath$).tw. or (familial idiopath$ adj2 cardiomyopath$).tw. or (cardiomyopath$ adj2 dilat$).tw. (17665)
15 Hypoplastic Left Heart Syndrome/ or (hypoplasti$ adj3 left heart syndrome$).tw. (2051)
16 Diabetic Foot/ or (diabet$ adj3 foot$).tw. or (diabet$ adj3 feet$).tw. (7001)
17 Spinal Cord Injuries/ or (spinal cord adj3 contusion$).tw. or (spinal cord adj3 injur$).tw. or (spinal cord adj3 trauma$).tw. or (spinal cord adj3 laceration$).tw. or (myelopath$ adj3 post-traumatic).tw. or (myelopath$ adj3 posttraumatic).tw. or (traumatic adj3 myelopath$).tw. or (spinal cord adj3 transection$).tw. (33613)
18 Cerebral Palsy/ or cerebral pals$.tw. or (diplegia$ adj2 spastic).tw. or little$ disease.tw. (18522)
19 Cerebellar Ataxia/ or (Incoordination$ adj3 cerebellar).tw. or Adiadochokin$.tw. or Hypermetria$.tw. or (Ataxia$ adj3 cerebellar).tw. or (cerebellar adj2 hemiataxia$).tw. or dysmetria$.tw. (6336)
20 Brain Injuries/ or (encephalopath$ adj3 post concussive).tw. or (traumatic adj3 encephalopath$).tw. or (brain adj3 laceration$).tw. or (trauma$ adj3 brain).tw. or (injur$ adj3 brain).tw. or (contusion$ adj3 brain).tw. or (cortical adj3 contusion$).tw. (57956)
21 Hypoxia-Ischemia, Brain/ or (Anoxi$ adj3 ischemia$).tw. or (hypoxi$ adj3 ischemi$).tw. (9085)
22 Brain Ischemia/ or Stroke/ or (Encephalopath$ adj3 ischemi$).tw. or (Ischemia$ adj3 cerebral).tw. or (Brain adj3 ischemi$).tw. or (chronic ischemi$ adj3 stroke).tw. (89138)
23 Amyotrophic Lateral Sclerosis/ or (disease adj2 guam).tw. or (Gehrig$ adj2 disease$).tw. or (amyotrophic adj4 lateral sclerosis).tw. or als.tw. or motor neuron disease.tw. (21881)
24 Diabetes Mellitus, Type 1/ or (Autoimmun$ adj3 diabet$).tw. or (Diabete$ mellitus adj4 sudden onset).tw. or (Diabete$ mellitus adj4 brittle).tw. or iddm.tw. or (diabetes mellitus adj5 insulin dependent).tw. or (ketosis prone adj4 diabetes mellitus).tw. or (juvenile onset adj5 diabete$ mellitus).tw. or (type 1 adj4 diabete$).tw. (72905)
25 Liver Cirrhosis/ or (Fibros$ adj3 liver).tw. or (Cirrhos$ adj2 hepatic).tw. or (Cirrhos$ adj2 liver).tw. (66791)
26 Thromboangiitis Obliterans/ or (Buerger$ adj2 disease$).tw. or thromboangitis obliterans.tw. (2841)
27 exp Eye Diseases/ or ocular surface disease$.tw. or ocular surface disorder$.tw. or asthenopia.tw. or cogan syndrome$.tw. or conjunctival disease$.tw. or corneal disease$.tw. (425213)
28 exp Hearing loss/ or Acquired hearing loss.tw. (51193)
29 Infant, Premature/ or premature$ infan$.tw. or preterm infan$.tw. or extremely low birth weight$.tw. (50626)
30 or/9-29 (1140445)
31 8 and 30 (2366)
32 clinical trial.pt. (476541)
33 exp clinical trial/ (705850)
34 randomized controlled trial.pt. (342317)
35 controlled clinical trial.pt. (85680)
36 randomi?ed.ab. (309312)
37 placebo.ab. (141651)
38 trial.ti. (111077)
39 exp Clinical Trials as Topic/ (264111)
40 multicenter study.pt. (152981)
41 exp epidemiologic studies/ (1487306)
42 (cohort adj2 (study or analysis)).tw. (72043)
43 (case adj2 (control$ or series or report$)).tw. (400611)
44 case reports.pt. (1609515)
45 or/32-44 (3879201)
46 31 and 45 (471)
47 animals/ not humans/ (3717560)
48 46 not 47 (451)
49 limit 48 to yr="1860 - 2012" (451)
50 ("20120726" or "20120727" or "20120728" or "20120729" or "20120730" or "20120731" or 201208$ or 201209$ or 201210$ or 201211$).ed. (460226)
51 49 not 50 (434)

Figure 1. Search Strategy used in Ovid MEDLINE(R) In-Process and Other Nonindexed Citations and Ovid MEDLINE(R), 1946 to present; limited to July 25, 2012.

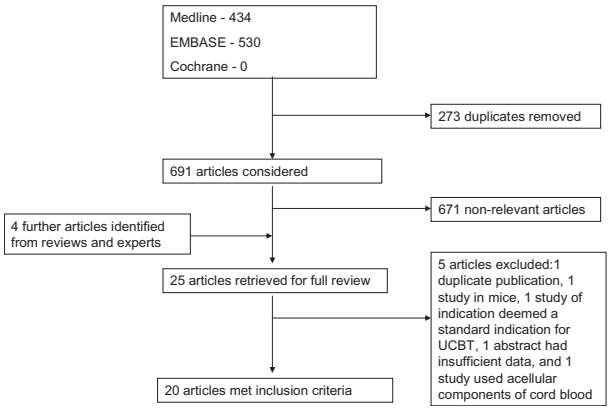

Figure 2. Summary of results from the systematic search strategy and identification of studies included for analysis.

week 26 of 2012), and (3) Cochrane (1950 to the second quarter of 2012), using the search strategy detailed in Figure 1. Specifically, the following search concepts were used: (1) umbilical cord transplantation, (2) regenerative medicine, and (3) specific diseases associated with potential success with UCB. To further augment our search, we attempted to identify any potential "grey" literature using Google Scholar. Reference lists of included studies were reviewed to identify additional published material. To identify ongoing registered clinical studies, the website www.clinicaltrials.gov and the search portal of the World Health Organization's International Clinical Trials Registry Platform (ICTRP) at http://www.who.int/ictrp/search/en/ were searched using broad terms for *umbilical cord blood, infusion,* and *transplantation* (performed March 1, 2013).

Information Analysis

All duplicates, editorials and opinion articles, review articles, studies involving animals, and articles that did not involve human UCB were removed. The process of selecting articles for inclusion and subsequent analysis was performed in duplicate (M.A.J.I. and D.S.A.). All relevant studies were first divided into published clinical trials or ongoing clinical trials, then further categorized based on disease process (ie, cardiovascular, diabetes, hepatic, etc.). Each paper was then analyzed for the following parameters: specific disease treated, patient age, geographic region of intervention, whether the cord blood units were banked in private or public establishments, relationship of patient to donor of banked cord blood unit (allogeneic or autologous), the route of administration of cells to the patient, and cell type and quantity (ie, total nucleated cells, MSCs, or other). These parameters were then tabulated and described.

RESULTS

Our search for published literature on clinical use of UCB for nonhematologic indications yielded a total of 691 publications after removing duplicates and excluding editorials, opinion articles, studies involving animals, and articles that did not involve human UCB (see Figure 2). In addition, articles describing the use of cord blood transplantation for hematopoietic disorders or inherited metabolic disorders were excluded, as these papers addressed accepted and/or standard indications for transplantation. A total of 25 articles were selected for full review and 5 articles were subsequently excluded on the basis of duplicate publication (1 study), standard indication for UCB transplantation (1 study describing X-linked chronic granulomatous disease), nonhuman transplant model (1 study), insufficient reporting of data (1 abstract), and the use of acellular components of cord blood (1 study). A total of 20 published articles describing the treatment of 317 patients, therefore, were included in our final analysis. Three of the studies were controlled (nonrandomized) [17-19], including a total of 115 patients (controls are not included in the patient totals for the studies described in Table 1). The most widely reported activity was the use of UCB-derived cells to treat neurological disorders [20-28] (total of 156 patients in 9 published studies), liver cirrhosis and hepatitis [17,19] (99 patients in 2 studies), and type 1 diabetes [18,29] (30 patients in 2 studies). A complete list of disorders described in published reports is provided in Table 1. In some cases, the UCB-derived cells were infused with the intent to repair damaged tissues [17,19-28,30-33] (15 studies, 260 patients), whereas in other patients, the cells were intended to facilitate immune modulation [18,29,34-36] (5 studies, 57 patients). Only 3 published reports had control groups (case controls or control groups in randomized trials) describing a total of 114 treated patients. Although the safety and feasibility of infusion were described in most reports, data suggesting possible clinical benefit were described in 15 studies reporting on outcomes of 179 treated patients. Possible benefit was reported in at least 1 report for each of the disease categories (see Table 1). Patient-specific data extraction was not performed and pooled analysis of data was not possible because of lack of controls and/or heterogeneity of the studies.

Our preliminary search of registered clinical studies revealed a total of 411 studies from www.clinicaltrials.com and 93 studies from the World Health Organization's ICTRP. After removing duplicates and screening for relevance, we identified a total of 47 ongoing registered clinical trials that address a wider spectrum of novel clinical indications for UCB-derived cell therapy (see Table 1 for complete list of studies). Within this group of 47 studies, 9 appeared in both registries. There is apparent increased activity in the use of UCB-derived cells for the treatment of neurological disorders (23 trials), with a total of 9 trials enrolling patients with cerebral palsy. Other ongoing trials reflect increased activity in the treatment of type 1 diabetes (7 trials) and liver cirrhosis (7 trials). The majority of ongoing trials address regenerative therapy (35 studies) as opposed to immunomodulatory therapy for autoimmune conditions (12 studies). The result of our search for ongoing studies using UCB-derived cells for regenerative therapy or immune modulation is provided in Table 1.

The majority of published and active trials involve adult patients or a combination of adult and pediatric patients, with only 7 published studies [22,24,27-29,32,33] (46 patients) and 17 ongoing studies enrolling only pediatric patients. (Table 2) Most patients described in published reports were treated in China [17,19,23,25,28,32,33,36] (8 studies, 261 patients), the United States [18,21,29,30] (4 studies, 32 patients), and Korea [20,24,34,35] (4 studies, 13 patients). Other countries that have published their observations of patients undergoing UCB-derived regenerative or immunomodulatory therapy are European countries [26,31] (2 studies involving 3 patients), Russia [22] (1 study involving 6 patients), and Thailand [27] (1 study involving 2 patients). Ongoing registered studies reflect a similar geographic distribution with the majority of registered studies coming from China (26 studies), the United States (9 studies), and Korea (6 studies). (Table 3)

The most common cell type described in published articles of UCB transplants is the administration of total nucleated cells, mononuclear cells, or CD34-selected hematopoietic progenitors [19,22,23,25-27,29,31,32,34] (10 studies, 227 patients), given either intravenously [19,22,23,26,27,29,32] (7 studies, 104 patients) or through intrathecal, subcutaneous, or intramuscular injection [25,31,34] (3 studies, 123 patients). MSCs or expanded adherent cells cultured ex vivo were infused intravenously in 5 published studies [17,18,28,33,36]

Table 1
Clinical Studies of Regenerative Therapy or Modulation of Refractory Autoimmune Disease Using Umbilical Cord Blood–Derived Cell Transplantation

Disease Categories	Published Studies			Registered Ongoing Studies
	Published (Patients)	Controlled Studies (Patients)	No. Reporting Possible Benefit (Patients)	n
Neurological	9 (156)	0	6 (40)	23
Spinal cord injury [20,21][*]	2 (2)	0	2 (2)	3
Traumatic brain injury [22][†]	1 (6)	0	1 (6)	4
Stroke [23,24][‡]	2 (11)	0	1 (10)	3
Neurodegenerative disorders [25,26][§]	2 (115)	0	0	2
Cerebral palsy, neonatal hypoxic-ischemic encephalopathy, and global developmental delay [27,28][‖]	2 (22)	0	2 (22)	9
Autism[¶]	0			1
Preterm neonates[#]	0			1
Diabetes mellitus	2 (30)	1 (15)	1 (15)	8
Type 1 diabetes mellitus [18,29][**]	2 (30)	1 (15)	1 (15)	7
Type 2 diabetes[††]	0			1
Cardiac and vascular	3 (12)	0	2 (5)	3
Thromboangiitis obliterans [34,35]	2 (11)	0	1 (4)	0
Critical limb ischemia[‡‡]	0			1
Hypoplastic left heart syndrome[§§]	0			1
Idiopathic dilated cardiomyopathy [30][‖‖]	1 (1)	0	1 (1)	1
Hepatic/gastrointestinal	2 (99)	2 (99)	2 (99)	9
Liver cirrhosis [17][¶¶]	1 (30)	1 (30)	1 (30)	7
Viral hepatitis [19][##]	1 (69)	1 (69)	1 (69)	1
Ulcerative colitis[***]	0			1
Dermatological	1 (2)	0	1 (2)	2
Skin wound [31], burn[†††]	1 (2)	0	1 (2)	1
Epidermolysis bullosa[‡‡‡]	0			1
Other	3 (18)	0	3 (18)	2
Rheumatoid arthritis[§§§]	0			1
Systemic lupus erythematosus [36][‖‖‖]	1 (16)	0	1 (16)	1
Duchenne muscular dystrophy [32,33]	2 (2)	0	2 (2)	0
Total	20 (317)	3 (114)	15 (179)	47

[*] NCT01046786, NCT01393977, NCT01471613.
[†] NCT01251003, NCT01451528, NCT01649648, ChiCTR-TNRC-11001528.
[‡] NCT01438593, NCT01673932, NCT01700166.
[§] NCT01489267, NCT01494480.
[‖] NCT00593242, NCT01072370, NCT01147653, NCT01193660, NCT01506258, NCT01528436, NCT01601158, NCT01649648, ChiCTR-TNC-11001486.
[¶] NCT01343511.
[#] NCT01121328.
[**] NCT00305344, NCT00873925, NCT00989547, NCT01143168, NCT01219465, NCT01374854, ACTRN12613000186752.
[††] NCT01413035.
[‡‡] NCT00518934.
[§§] NCT01445041.
[‖‖] NCT01739777.
[¶¶] NCT1220492, NCT01224327, NCT01491165, NCT01342250, NCT01573923, NCT01718587, ChiCTR-TNRC-11001488.
[##] NCT01724398.
[***] NCT01221428.
[†††] NCT01443689.
[‡‡‡] NCT01033552.
[§§§] NCT01547091.
[‖‖‖] NCT01741857.

(82 patients) or given through intrathecal or intramuscular injection [20,24,35] (3 studies, 6 patients), whereas combined therapy using CD34-selected cells with MSCs expanded from UCB was described in 2 case reports [21,30] (2 patients) using either intravenous infusion [30] (1 patient) or intrathecal injection [21] (1 patient). (Table 4) The majority of published studies describe the use of cord blood–derived cells from allogeneic sources (18 studies, 300 patients), whereas only 2 studies [27,29] (10% of studies; 17 patients, or 5.4% of patients) used autologous cells. Ongoing registered clinical trials, however, describe increasing use of autologous cells (13 studies, or 28% of registered studies).

Table 2
Populations Treated with UCB Stem Cells

Patient Population	Published (Patients)	Ongoing Studies, n
Pediatric	7 (46)	17
Adult	11 (142)	24
Pediatric and adult	2 (129)	6

UCB indicates umbilical cord blood.

DISCUSSION

Analysis of the published literature and ongoing registered clinical studies reveals a broad range of diseases treated with UCB-derived cellular products. The most commonly published area of expertise in the use of UCB-derived cellular transplantation for regenerative and immunomodulatory therapy is for neurological disorders, and this remains the most active area of study in ongoing registered trials. An increasing range of disorders, however, is reflected in the ongoing registered trials, which suggests increasing activity, interest, and investment in UCB-derived cellular therapy. Interestingly, adult patients compose the majority of patients

Table 3
Geographic Regions Treated with UCB Stem Cells

Geographic Region	Published (Patients)	Ongoing Studies, n
China	8 (261)	26
United States	4 (32)	9
Korea	4 (13)	6
European Union + United Kingdom	2 (3)	1
Thailand	1 (2)	0
Russia	1 (6)	0
Egypt	0	1
Mexico	0	1
Singapore	0	1
South America	0	1
Australia	0	1

UCB indicates umbilical cord blood.

reported in published reports and registered ongoing clinical studies continue to enroll predominantly adult subjects. Geographically, Asian countries appear most active in UCB-derived cellular therapy and our analysis of ongoing studies suggests this trend will likely continue.

Most reported studies infused unprocessed bulk cells from UCB that was processed and cryopreserved in accordance with standard UCB banking practices. These studies reported total nucleated cell numbers and other standard measures of hematopoietic stem cells including CD34+ cell numbers and colony-forming units. MSCs expanded ex vivo from freshly collected cells were another cell type reported commonly in published studies. MSCs were reported in published trials of tissue regeneration and in studies of immune dysregulation. Interestingly, recent work suggests that MSCs can only be expanded successfully from 30% to 60% of UCB units [37], although newer approaches of collecting cells from Wharton's jelly or from the placenta itself enhances the yield of MSC expansion from UCB [38]. Although most published reports involved adults, the treatment of adult patients using UCB cells continues to be limited in part by the total dose of cells per kilogram that can be delivered from a single unit. Cell losses during processing and cryopreservation can further reduce the number of available cells and can limit the ability to culture and expand MSCs using cryopreserved units [39]. Moreover, the majority of patients described in published reports received HLA-compatible cord blood cells or third party MSCs that were expanded ex vivo. There may be increasing use of autologous cells in the future, given the presence of autologous cord blood banking establishments and increasing interest in the area of autologous cord blood transplantation for pediatric patients with cerebral palsy. The results of ongoing studies will be informative and will likely shape future directions in autologous cord blood banking practices.

Table 4
Cell Types Derived from UCB Used in Treatment for Nonhematopoietic Diseases

Cell Type Administered	Published (Patients)	Ongoing Studies, n
TNCs, MNCs, or CD34-selected cells	10 (227)	19
Intravenous (or not stated)	7 (104)	15
Intrathecal, subcutaneous, or intramuscular	3 (123)	4
MSC or cultured adherent cells	8 (88)	24
Intravenous (or not stated)	5 (82)	24
Intrathecal or intramuscular	3 (6)	0
Combined CD34-selected cells and MSCs	2 (2)	4
Intravenous (or not stated)	1 (1)	4
Intrathecal	1 (1)	0
Cell source	20 (317)	47
Allogeneic cells	18 (300)	34
Autologous cells	2 (17)	13

UCB indicates umbilical cord blood; TNC, total nucleated cells; MNC, mononuclear cells; MSC, mesenchymal stromal cells.

A limitation of scoping reviews, including ours, is the possibility that we did not encompass all published and ongoing trials. We attempted to reduce this error by searching 3 large scientific databases (Medline, Embase, and Cochrane Library) using broad key words and key phrases, without language restriction. The search results were double-checked to ensure all relevant studies were identified. The possibility remains, however, that our search criteria failed to capture pertinent publications. With regard to ongoing registered studies identified using www.clinicaltrials.gov and the ICTRP of the World Health Organization, it is possible that additional studies were not registered or were registered with other registries.

In summary, our scoping review provides a synopsis of the emerging clinical activity in UCB transplantation for regenerative and immunomodulatory therapy. In addition, there is increasing activity in the areas of correcting immune dysregulation that leads to autoimmune disease and inflammatory conditions, and the use of MSCs derived from UCB is an area of increasing expertise. The United States and China continue to lead in knowledge generation related to the use of UCB; however, the extent to which clinical practice in these jurisdictions can be applied elsewhere remains to be examined. Moreover, transplantation into adult patients will continue with significant projected enrollment in ongoing trials. Regular assessment of published and ongoing activity in UCB transplantation for emerging novel indications will be critical for informing UCB banking establishments and funding agencies to guide changes in banking practices related to emerging trends in cell therapy.

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REFERENCES

1. Cohen Y, Nagler A. Umbilical cord blood transplantation—how, when and for whom? *Blood Rev*. 2004;18:167-179.
2. Martin PL, Carter SL, Kernan NA, et al. Results of the Cord Blood Transplantation Study (COBLT): Outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with lysosomal and peroxisomal storage diseases. *Biol Blood Marrow Transplant*. 2006;12:184-194.
3. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med*. 2004;351:2276-2285.
4. Gluckman E, Broxmeyer HA, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med*. 1989;321:1174-1178.
5. McKenna D, Sheth J. Umbilical cord blood: Current status and promise for the future. *Indian J Med Res*. 2011;134:261-269.
6. Berger MJ, Adams SD, Tigges BM, et al. Differentiation of umbilical cord blood-derived multilineage progenitor cells into respiratory epithelial cells. *Cytotherapy*. 2006;8:480-487.
7. Yang C, Zhang ZH, Li ZJ, et al. Enhancement of neovascularization with cord blood CD133+ cell-derived endothelial progenitor cell transplantation. *Thromb Haemost*. 2004;91:1202-1212.
8. Ingram DA, Mead LE, Tanaka H, et al. Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood. *Blood*. 2004;104:2752-2760.

9. Kogler G, Sensken S, Airey JA, et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J Exp Med*. 2004;200:123-135.
10. Chen N, Hudson JE, Walczak P, et al. Human umbilical cord blood progenitors: The potential of these hematopoietic cells to become neural. *Stem Cells*. 2005;23:1560-1570.
11. Broxmeyer HE, Lee MR, Hangoc G, et al. Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21- to 23.5-year cryopreserved cord blood. *Blood*. 2011;117:4773-4777.
12. van de Ven C, Collins D, Bradley MB, et al. The potential of umbilical cord blood multipotent stem cells for nonhematopoietic tissue and cell regeneration. *Exp Hematol*. 2007;35:1753-1765.
13. McCullough J, McKenna D, Kadidlo D, et al. Issues in the quality of umbilical cord blood stem cells for transplantation. *Transfusion*. 2005; 45:832-841.
14. American Association of Blood Banks. *Standards for cellular therapy product services*, 2nd ed. Bethesda, MD: American Association of Blood Banks; 2007.
15. Net Cord Foundation for the Accreditation of Cellular Therapy. *Internal standards for cord blood collection, processing, testing, banking, selection and release*, 3rd ed. Bethesda, MD: American Association of Blood Banks; 2006.
16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
17. Zhang Z, Lin H, Shi M, et al. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. *J Gastroenterol Hepatol*. 2012;27(Suppl 2): 112-120.
18. Zhao Y, Jiang Z, Zhao T, et al. Reversal of type 1 diabetes via islet b cell regeneration following immune modulation by cord blood-derived multipotent stem cells. *BMC Med*. 2012;10:3.
19. Tang XP, Yang X, Tan H, et al. Clinical and experimental study on therapeutic effect of umbilical cord blood transplantation on severe viral hepatitis. *World J Gastroenterol*. 2003;9:1999-2003.
20. Kang KS, Kim SW, Oh YH, et al. A 37-year-old spinal cord-injured female patient, transplanted of multipotent stem cells from human UC blood with improved sensory perception and mobility, both functionally and morphologically: A case study. *Cytotherapy*. 2005;7:368-373.
21. Ichim TE, Solano F, Lara F, et al. Feasibility of combination allogeneic stem cell therapy for spinal cord injury: A case report. *Int Arch Med*. 2010;3:30.
22. Fufaeva E, Semenova J, Semenova N, Sidorin S. Dynamics of high mental function recovery in children after severe traumatic brain injury having umbilical cord blood cells therapy. *Brain Inj*. 2012;26: 688-689 [abstract].
23. Man Y, Li J, Yang B, Ma J. Vein transplantation using human umbilical cord blood stem cells in the treatment of stroke sequela. *Neural Regener Res*. 2006;1:618-621.
24. Han H, Chang SK, Chang JJ, Hwang SH. Intrathecal injection of human umbilical cord blood. *J Med Case Reports*. 2011;5:562.
25. Yang WZ, Zhang Y, Wu F, et al. Safety evaluation of allogeneic umbilical cord blood mononuclear cell therapy for degenerative conditions. *J Transl Med*. 2010;8:75.
26. Cordes AL, Jahn K, Hass R, et al. Intramedullary spinal cord implantation of human CD34+ umbilical cord-derived cells in ALS. *Amyotrophic Lateral Sclerosis*. 2011;12:325-330.
27. Papadopoulos KI, Low SSS, Aw TC, Chantarojanasiri T. Safety and feasibility of autologous umbilical cord blood transfusion in 2 toddlers with cerebral palsy and the role of low dose granulocyte-colony stimulating factor injections. *Restor Neurol Neurosci*. 2011;29:17-22.
28. Wu F, Yang J-Y, Zhang M, et al. Effect of umbilical cord blood mesenchymal stem cell transplantation on nervous system function in 20 cerebral palsy children. *J Clin Rehab Tissue Eng Res*. 2008;12:3198-3200.
29. Haller MJ, Wasserfall CH, Hulme MA, et al. Autologous umbilical cord blood transfusion in young children with type 1 diabetes fails to preserve C-peptide. *Diabetes Care*. 2011;34:2567-2569.
30. Ichim TE, Solano F, Brenes R, et al. Placental mesenchymal and cord blood stem cell therapy for dilated cardiomyopathy. *Reprod Biomed Online*. 2008;16:898-905.
31. Valbonesi M, Giannini G, Migliori F, Costa RD. Cord blood (CB) stem cells for wound repair. *Transfus Apher Sci*. 2004;30:153-156.
32. Zhang C, Feng HY, Huang SI, et al. [Therapy of Duchenne muscular dystrophy with umbilical cord blood stem cell transplantation]. *Chin J Med Genet* [Chinese]. 2005;22:399-405.
33. Yang X-F, Xu Y-F, Lu N-W, et al. Stem cell transplantation in sequence for treatment of Duchenee muscular dystrophy. *J Clin Rehab Tissue Eng Res*. 2010;14:7487-7492.
34. Kim AK, Kim MH, Kim S, et al. Stem-cell therapy for peripheral arterial occlusive disease. *Eur J Vasc Endovasc Surg*. 2011;42:667-675.
35. Kim SW, Han H, Chae GT, et al. Successful stem cell therapy using umbilical cord blood-derived multipotent stem cells for Buerger's disease and ischemic limb disease animal model. *Stem Cells*. 2006;24:1620-1626.
36. Sun L, Wang D, Liang J, et al. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum*. 2010;62:2467-2475.
37. Watt SM, Contreras M. Stem cell medicine: Umbilical cord blood and its stem cell potential. *Semin Fetal Neonatal Med*. 2005;10:209-220.
38. Montanucci P, Basta G, Pescara T, et al. New simple and rapid method for purification of mesenchymal stem cells from the human umbilical cord Wharton jelly. *Tissue Eng Part A*. 2011;17:2651-2661.
39. Kögler G, Critser P, Trapp T, Yoder M. Future of cord blood for non-oncology uses. *Bone Marrow Transplant*. 2009;44:683-697.